REMARKS

Claims 4 - 10 have been withdrawn subject to the possibility of rejoinder if claims 1 and 2 are found to be allowable.

Turning now to the enablement issue, the most recent case to address these issues was that of *Chiron Corporation v. Genentech, Inc* (70 USPQ2d 1321 (Fed. Cir. 2004). In concluding that in such circumstances the enablement requirement had been met, the Federal Circuit based its decision on the non-existence of any chimeric antibody at the relevant date. This is not the present situation. The applicants have described specific embodiments and, as noted above, submit that the production of other embodiments is within the competence of those skilled in the art. In reaching its decision, the Federal Circuit observed that it is not required that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art. (citing *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). Nascent technology of the type confronted in the *Chiron* case must, however, must be enabled with a "specific and useful teaching." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1368 (Fed. Cir. 1997).

Prior to looking at the application of the Wands factors to the present application, it should be recalled that the Federal Circuit has made it clear in *PPG Industries v. Guardian Indus. Corp* 75 F.3d 1558 (Fed. Cir. 1996), that "the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the experimentation must not be unduly extensive".

The first point to note is that the specification is addressed to one skilled in the art who is presumed to know and understand at least the prior art acknowledged in the present application. In considering the present issue, the Examiner seems to have ignored the fact that in seeking to put the present invention into practice, the skilled worker is not simply groping around in the dark. Acetylcholinesterase inhibitors are a well known class of compounds as is

shown by the enclosed pages from Burger's Medicinal Chemistry and Drug Discovery (Fifth Edition) Volume 2 pages 42 - 52. The question of whether such a compound has a central effect (that is can pass the blood-brain barrier) and the half life of the compound in the body can be determined by standard experimental techniques.

Turning now to the Wands factors themselves, the factors to be considered are:

(1) the quantity of experimentation necessary: the examiner hypothesizes that an exhaustive search is needed. The applicant's disagree. The compounds to be used form a known class of compounds from which a selection can be made.
(2) the amount of direction or guidance provided: the specification describes several types of useful compounds to assist the skilled reader in his or her selection;
(3) the presence or absence of working examples: it is agreed that none are provided
(4) the nature of the invention: essentially a new use of a known class of compounds;
(5) the state of the prior art: the invention is in a developing field; not one that is nascent;
(6) the relative skill of those in the art: high;
(7) the predictability or unpredictability of the art: becoming developed; and
(8) the breadth of the claims: relatively narrow.

Even applying the Wands factors therefore, it is submitted that the present specification provides one skilled in the art to produce and use the claimed receptors throughout the breadth of the claims.

It is therefore submitted that the enablement requirement has been met.

Turning now to the 35 USC 102 rejection, it is agreed that in some circumstances a use may be inherent and so anticipate a later claim to that inherent use. However, that is not the case here. The issue in Ex parte Novitski was one of preventing something from happening, namely nematode infestation of plants. Plants had previously been treated with a bacterium specified in the claim for another purpose and did not become infested. Contrary to the examiners supposition, the claims in the present application are not directed to the prevention of anything. Claim 1 is directed to treating conditions that can benefit from stimulation of the HPG axis.

Nothing in the prior art shows the likelihood that prior use of acethylcholinesterase inhibitors would have resulted in treatment of such a condition. Prior use has been primarily for treatment of Alzheimer's disease, a disease of the elderly. The conditions that result from a lack of stimulation of the HPG axis that are susceptible of treatment in the present invention are not conditions of the elderly. This is particularly true of the condition specified in claim 3. In any case to be a treatment of a disease in a patient suffering from a specified disease, there must be a determination of the existence of the disease in the patient. Nothing inherently meets this requirement. Either such a determination has been made or it has not been.

Having regard to the 35 USC 103 rejection, the examiner argues that the references Hinz, Saiko and Walles teach that the specified c compounds will induce ovulation and decrease sexual maturation time. The applicant respectfully disagrees. The present invention is essentially directed to use of acetlycholinesterase inhibitors to stimulate the HPG axis by influencing the secretion of gonadotropin releasing hormone. As explained on pages 8 - 12 of the specification, such treatments typically require administration of the specified compounds for several weeks at least.

The advantages of the present invention are made clear by the attached articles from Goodman and Gilman's Pharmacological Basis of Therapeutics and two chapters from issues of Endocrinology and Metabolism Clinics of North America.

The Goodman and Gilman chapter addresses GnRH mostly only on page 1379. In the male, testicular growth, attainment of normal male steroid levels and spermatogenesis are discussed. Promoting testicular descent is also mentioned. For the female, normal steroid levels, achievement of ovulation and menstruation are noted.

Moghissi's article describes the use of GnRH preparations, and points out that stimulatory uses have to be achieved via portable pulsatile infusion pumps. Superagonist treatments, which downregulate, are not of interest. It is noted that "Subcutaneous therapy usually requires larger doses of GnRH and is less successful than intravenous therapy....No serious adverse effects have been observed with subcutaneous therapy. However, during

intravenous therapy, severe complications, such as bacteremia with high fever and phlebitis, have been reported occasionally."

Thus, treatment with a cholinesterase inhibitor offers a significant therapeutic advantage.

Matsumoto discusses the hormonal therapy of male hypogonadism. GnRH is cited in Table 1, page 861, for the treatment of adult hypogonadism, to initiate and maintain spermatogenesis, and for delayed puberty. The GnRH section begins on page 871. They also discuss the difficulty and potential complications, concluding, "Because of the greater complexity associated with long-term pulsatile GnRH treatment, it is usually reserved for intelligent, highly motivated, compliant and reliable men with IHH who can manage the problems and inconvenience of chronic infusion pump therapy or for those who do not respond to gonadotropin therapy." (p.872).

Administration of the compounds specified in the present claims is much simpler.

Turning now to the cited art, both Hinz and Walles are acute experiments in which increased acetylcholine is associated with the extrusion of the egg from the follicle. Hinz describes, in rabbits, the post-coital increase of ACh and acetylcholinesterase in blood, ascribing to these stimulation of the "release of the egg from the follicle." Rabbits, but not humans, are reflex ovulators. Walles et al produce contraction in cat, cow and human ovarian follicular strips with ACh. Thus extrusion of the egg may have a cholinergic component.

The present application describes stimulation of the neuroendocrine control of ovulation by the specified compounds. Claim 3 claims use of the compounds to overcome failures of ovulation by stimulation of the HPG axis. According to the "Ovulation Stimulation and Induction" article by Blacker, which we have previously cited and submitted, "although clomiphene citrate is believed to have an antiestrogenic role at the level of the hypothalamus, an interaction with the pituitary has not conclusively been excluded. . . These findings imply that the ovulation inducing property of clomiphene citrate is exerted, at least partly, at the level of the hypothalamus." p. 63 Thus, references showing that extrusion of the egg could be promoted by acetylcholine do not address the two to three weeks before ovulation when the follicle is growing

an egg large enough for ovulation. This process is dependent on LH, which is released by LRH, which is stimulated by acetylcholine. A much more prolonged stimulation is required. All that one could do, based on the prior art, is to give a short treatment of a cholinergic drug at the time that there is a ripe egg. The claimed method gives the cholinergic agent for a period long enough to promote follicular development to the point where ovulation is possible and appropriate.

The Hinz article was cited as inducing ovulation and inducing sexual maturity. The examiner argues that such properties would motivate the skilled artisan to employ these compounds to positively effect sexual function generally. This contrasts with the view of the examiner in the International Preliminary Examination Authority who felt the available prior art did not disclose the use of acetylcholinesterse inhibitors in diseases of the HPG axis. He felt that Hinz, the "closest prior art," reported that "pyridostigmine anticipates puberty and increases male sexual behaviour in rats but this does not appear to be related to a 'condition than can benefit from a stimulation of the hypothalamic-pituitary-gonadal-axis.' Therefore, the man skilled in the art could not derive the claimed use from the indication given in D1." It is, of course open to different skilled persons to come to different conclusions as to the obviousness of a particular proposal. However, it is submitted that the logic of the Examiner in the IPEA is the more persuasive in the present situation.

The applicant did claim that the specified compounds could stimulate puberty. But the present application specified their use in patients "whose gonads and pituitary glands are responsive to GnRH." Hinz gave them for the first 14 days of rat life, with puberty occurring then at 37 days in the female, 80 in the male. Neonatal pyridostigmine advanced puberty by 1.5 days in females, 10 days in males. Our patients would be first evaluated when puberty did not occur within the normal time frame. If they were rats, this would then have been well after the neonatal treatment period used by Hinz. Conversely, the Hinz treatment corresponds to humans from several months before birth (rats are born earlier in development) until approximately 2 to 4 years old. At that age, one would not even know there is going to be a treatment required. Moreover, treatment to advance puberty when the future is not known, administered to babies, would be unthinkable to those skilled in the art.

In the absence of any teaching in the prior art that acetyl cholinesterase inhibition would assist in stimulating the HPG axis, it is irrelevant if the prior art indicates that increasing acetyl choline levels would otherwise enhance ovulation. This is not the invention claimed.

In view of the foregoing, it is submitted that this application is now in order for allowance and an early action to this end is respectfully solicited.

Respectfully submitted,

John Richards
LADAS & PARRY
26 West 61st. Street
New York, New York 10023
Reg. 31053
Tel. (212) 708-1915